REMARKS

Applicants respectfully request reconsideration and reexamination of the present application in light of the amendments and the remarks below.

Claims 1, 5-10, and 12-26 are pending in this application. Applicants elect 2-[2-ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f]-[1,2,4]-triazin-4-one as the PDE inhibitor and HMG-CoA-reductase inhibitors as the antilipemic species, as directed to claims 1, 5-10, and 12-26, for further prosecution in this application (Response to Restriction Requirement, mailed October 31, 2003). Claims 2-4 were cancelled in a Preliminary Amendment (submitted March 13, 2002).

Claims 5, 6, 18, and 19 have been amended. These claim amendments are made to clarify the subject matter therein. Therefore, these amendments are submitted in order to place the claims in condition for allowance, and do not disclaim any subject matter to which the Applicants are entitled.

Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 18 and 19 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention (Paper No. 20031124, page 2). Applicants respectfully traverse this rejection.

The Examiner stated that with regard to claim 18, the term "functional unit" is indefinite since it is not clear what are the metes and bounds of the term "functional" since it is not defined in the specification. Claim 18 has been amended accordingly. Specifically, claim 18 no longer recites the term "functional."

The Examiner stated that with regard to claim 19, the parenthetical term "spatially" is indefinite since it is not clear the term is in fact the claim limitation. Claim 19 has been amended accordingly. Specifically, claim 19 no longer recites the term "spatially."

It is thus submitted that the claims 18 and 19 meet the requirements of 35 USC § 112, second paragraph, and reconsideration and withdrawal of the present rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

The Examiner rejected claims 1, 5, 7-10, 12-18, and 20-26 under 35 U.S.C. § 103(a) as unpatentable over Liao, et al., (U.S. Patent No. 6,147,109) in view of Niewohner, et al., (WO 99/24433) of record (Paper No. 20031124, pages 3-5). Applicants respectfully traverse.

To properly maintain a rejection under 35 U.S.C. § 103, three conditions must be met. First, the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the prior art must also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of

success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in the Applicant's disclosure. Finally, the prior art reference must teach or suggest all the claim limitations. *See In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

The present invention is directed to the combination of PDE inhibitors and HMG-CoA reductase inhibitors and methods of treatment.

The Examiner states that Liao, et al., discloses that "HMG-CoA reductase inhibitors can be co-administered with a second agent with a condition treatable by the second agent in an amount effective to treat the condition to enhance the result." The Examiner also states that Liao, et al., "teach that the reductase inhibitor is administered simultaneously with the second agent close enough in time whereby the two compounds may exert an additive or even synergistic effect" (Paper No. 20031124, page 4).

In fact, the disclosure by Liao, et al., is a mere proposal to try any combination of pharmaceutical agents to treat any condition. Liao, et al., discloses a list of unrelated disorders (*see, e.g.,* column 7 and 8 of the specification) and a list of general categories of pharmaceutical agents (*see, e.g.,* column 13 and 14 of the specification). There is no suggestion to one of ordinary skill in the art that by combining an HMG-CoA reductase inhibitor with one of these pharmaceutical agents, one would have a reasonable expectation of success, that is, treating a particular disease. As one skilled in the art can easily appreciate, the failure rate in drug development is extremely high. More likely than not, toxicity or an adverse event is observed during the development of a therapeutic. And the likelihood of toxicity may be even higher when drugs are combined as a therapeutic. For example, there is the possibility of drug-to-drug interactions which can lead to serious side effects. Thus, the mere proposal to try any combination of pharmaceutical agents to treat a disease does not provide the requisite reasonable expectation of success, that is, a safe and efficacious theraputic. Moreover, as mentioned above, both the suggestion and the reasonable expectation of success must be adequately founded in the prior art.

Furthermore, the categories of pharmaceutical agents are very broad, for example, an "amino acid" or an "inhibitor." Obviously, one skilled in the art would not be motivated to combine, for example, an HMG-CoA reductase inhibitor with an amino acid or an inhibitor with the expectation of successful treatment of any disorder. Thus, one skilled in the art would not have the reasonable expectation that any combination of an HMG-CoA reductase inhibitor and any pharmaceutical agent as disclosed by Liao, et al., would lead to a successful treatment.

Liao, et al., also does not teach or suggest the combination of PDE inhibitors and HMG-CoA reductase inhibitors. As discussed above, Liao, et al., discloses a list of general categories of pharmaceutical agents; however, Liao, et al., does not teach or suggest PDE inhibitors as pharmaceutical agents. Therefore, based on the disclosure by Liao, et al., one of ordinary skill in the art would not have

been motivated to select a PDE inhibitor in combination with an HMG-CoA reductase inhibitor with the reasonable expectation of successful treatment of sexual dysfuntion.

With respect to additive or synergistic effects, again the disclosure by Liao, et al., is a mere proposal to try any combination of pharmaceutical agents and there may be an additive or synergistic effect. There is no suggestion to one of ordinary skill in the art that by combining an HMG-CoA reductase inhibitor with one of these pharmaceutical agents, one would have a reasonable expectation of success, that is, the two agents will have an additive or synergistic effect. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art. Obviously, the requisite reasonable expectation of success is lacking in the disclosure of Liao, et al.

The deficiencies of Liao, et al., are not remedied by Niewohner, et al. Niewohner, et al., discloses PDE inhibitors; however, Niewohner, et al., does not teach or suggest the combination of PDE inhibitors and HMG-CoA reductase inhibitors. Furthermore, based on the disclosure of Niewohner, et al., one skilled in the art would not have been motivated to combine PDE inhibitors and HMG-CoA reductase inhibitors to treat sexual dysfuntion.

It is therefore submitted respectfully that Liao, et al., either singly or in combination with Niewohner, et al., fails to teach or suggest the combination of PDE inhibitors and HMG-CoA reductase inhibitors, and methods of treatment as presently claimed, and that the current invention is novel and nonobvious in view of the prior art references.

The Examiner rejected claims 6 and 19 under 35 U.S.C. § 103(a) as unpatentable over Liao, et al., (U.S. Patent No. 6,147,109) in view of Niewohner, et al., (WO 99/24433) of record as applied to claims 1, 5, 7-10, 12-18, and 20-26, and further in view of Doherty, et al., (U.S. Patent No. 6,037,346) (Paper No. 20031124, pages 5-6). Applicants respectfully traverse.

The present invention is directed to a kit comprising the combination preparation of PDE inhibitors and HMG-CoA reductase inhibitors, and methods of treatment.

The Examiner stated that the "Teachings of Liao et al. and Niewohner et al. as applied as before" and that Liao, et al., and Niewohner, et al., "do not expressly teach the kit set forth in claims 6 and 19." The Examiner also stated that Doherty, et al., "teach the kit for the erectile dysfunction comprising PDE inhibitors and different active agents" (Paper No. 20031124, page 5).

As discussed above, neither Liao, et al., nor Niewohner, et al., teach or suggest the combination of PDE inhibitors and HMG-CoA reductase inhibitors, and the requisite reasonable expectation of success is lacking. Doherty, et al., does not teach or suggest the combination of PDE inhibitors and HMG-CoA reductase inhibitors. Doherty, et al., mentions additional active agents, but there is no suggestion to

combine PDE inhibitors with HMG-CoA reductase inhibitors. Both the suggestion and the reasonable expectation of success are lacking in Doherty, et al.

Therefore, based on the disclosures of Liao, et al., Niewohner, et al., and Doherty, et al., it would not have been obvious to one skilled in the art to prepare a kit comprising the combination of PDE inhibitors and HMG-CoA reductase inhibitors.

It is therefore respectfully submitted that Liao, et al., Niewohner, et al., and Doherty, et al., fail to teach or suggest the kits as presently claimed, and that the current invention is novel and nonobvious in view of the prior art references. For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the present rejection.

The Examiner rejected claims 1, 5, 7-10, 12-18, and 20-26 under 35 U.S.C. § 103(a) as unpatentable over Liao, et al., (U.S. Patent No. 6,147,109) in view of R & D Drug News (1998) (Paper No. 20031124, pages 6-7). Applicants respectfully traverse.

The Examiner stated that "Liao et al.'s teachings as applied before." The Examiner also stated that Liao, et al., "does not expressly teach the vardenafil and its specified salt (i.e. trihydrate)." In addition, the Examiner also stated that R & D Drug News "teaches vardenafil is the phosphodiesterase inhibitor in preclinical trials as a potential therapy for erectile dysfunction" (Paper No. 20031124, page 6).

The present invention is directed to the combination of PDE inhibitors and HMG-CoA reductase inhibitors and methods of treatment.

As discussed above, Liao, et al., does not teach or suggest the combination of PDE inhibitors and HMG-CoA reductase inhibitors, and the requisite reasonable expectation of success is lacking.

The deficiencies of Liao, et al., are not remedied by R & D Drug News. R & D Drug News discloses vardenafil; however, R & D Drug News does not teach or suggest the combination of vardenafil and HMG-CoA reductase inhibitors. Furthermore, based on the disclosure of R & D Drug News one skilled in the art would not have been motivated to combine vardenafil and HMG-CoA reductase inhibitors and the requisite reasonable expectation of success is lacking.

It is therefore respectfully submitted that Liao, et al., and R & D Drug News fail to teach or suggest the invention as presently claimed, and that the current invention is novel and nonobvious in view of the prior art references. For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the present rejection.

The Examiner rejected claims 6 and 19 under 35 U.S.C. § 103(a) as unpatentable over Liao, et al., (U.S. Patent No. 6,147,109) in view of R & D Drug News as applied to claims 1, 5, 7-10, 12-18, and 20-26, and further in view of Doherty, et al., (U.S. Patent No. 6,037,346) (Paper No. 20031124, pages 7-8). Applicants respectfully traverse.

The Examiner stated that "Liao, et al., and R & D Drug News do not expressly teach the kit set forth in claims 6 and 19" (Paper No. 20031124, page 7).

As discussed above, neither Liao, et al., nor R & D Drug News teach or suggest the combination of PDE inhibitors and HMG-CoA reductase inhibitors, and the requisite reasonable expectation of success is lacking. In addition, as discussed above, Doherty, et al., does not teach or suggest the combination of PDE inhibitors and HMG-CoA reductase inhibitors. In fact, Doherty, et al., lacks both the suggestion and the reasonable expectation of success.

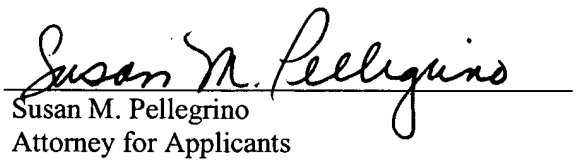
It is therefore respectfully submitted that Liao, et al., R & D Drug News, and Doherty, et al., and fail to teach or suggest the invention as presently claimed, and that the current invention is novel and nonobvious in view of the prior art references. For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

For the foregoing reasons, Applicants submit that the claims are in condition for allowance and Applicants respectfully request reexamination of the present application, reconsideration and withdrawal of the present rejections, and entry of the amendments. Should there be any further matter requiring consideration, Examiner Kim is invited to contact the undersigned counsel.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 13-3372. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should also be charged to undersigned's deposit account.

Respectfully submitted,



Susan M. Pellegrino
Attorney for Applicants
Reg. No. 48,972

Date: March 5, 2004

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Telephone: (203) 812-6450
Facsimile: (203) 812-6459